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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,570	11/28/2000	Dale B. Schenk	209-US-NEW6	6101

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/724,570	SCHENK, DALE B.	
	Examin r	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *11-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election **without** traverse of Group I (claims 1-10) drawn to a pharmaceutical composition of prior precursor protein in Paper No. 3 (16 May 2003) is acknowledged. Claims 11-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Specification

2. The specification is objected to because of the following informalities: Please delete the phrase "[REMAINDER PAGE INTENTIONALLY BLANK]" (pp. 88, 98, and 100); page 96 is missing. Appropriate correction is required.

Drawings

3. The drawings are objected to because: Figure 11 does not contain a legend to define the symbols used; the brief description in the disclosure for Figure 15 does not contain a description of each part (A-E); the figure title for Figure 16 is mislabeled as "AB" and not "A-beta" or "Aβ". A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claims 1-10 are objected to because of the following informalities: specifically recite non-elected material. Appropriate correction is required.

Claim Rejections - 35 USC § 101

Double Patenting

> A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).
>
> A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Claims **1-10** are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-10 of copending Application No.'s 09/585817, 09/724953, 09/724567, and 09/724575. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

6. Claims **1-10** of this application conflict with claims **1-10** of Application No.'s 09/585817, 09/724953, 09/724567, and 09/724575. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either

cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

7. Claims **1-10** are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-57 of copending Application No. 09/979952. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

8. Claims **1-10** of this application conflict with claims **1-10** of Application No. 09/979952. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Non-Statutory Obvious-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims **1-10** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of Application 09/497553, claims 44-45, 48, and 67-70 of Application 09/723927, claims 102-109 of Application 09/724489, claims 38, 40, 42-52, and 56-59 of Application 09/723760, claims 3-6, 8-9, and 12-13 of Application 09/724921, claims 3-6, 8-9, and 12-13 of Application 09/724929 in view of Sipe (1992) "Amyloidosis" Annu. Rev. Biochem. **61**: 947-975 and US 5780587.

10. Concerning diseases characterized by amyloid deposits, several neurodegenerative diseases, including but not limited to Alzheimer's disease and prion diseases, have the motif insoluble deposits of protein, known as plaques, aggregates, or fibrils, that are held to be key to the cause of the particular malady. The inhibition or elimination of said insoluble deposits of proteins at the time of the invention was seen as a desirable method by which said malady could be treated or a way to alleviate symptoms [Sipe (1992) & US 5780587].

11. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of 09/497553, 09/723927, 09/724489, 09/723760, 09/724921 and 09/724929, are drawn to **pharmaceutical compositions**, comprising an agent effective to induce an immune response against an amyloid component in a patient, including but not limited to amyloid proteins and immunogenic fragments, thus meeting the limitations of claims 1-10 of the instant Application 09/724570.

12. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims **1-10** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

14. The instant claims are drawn quite broadly to a pharmaceutical composition comprising an agent effective to induce an immune response against an amyloid component in a patient wherein the agent is prior precursor protein (PrP). The language of said claims encompasses therapeutic use of said pharmaceutical composition for any amyloid related disease or disorder. It is noted that the instant Specification defines "AScr" as PrP^{Sc} or the infectious/pathological form of PrP (pp. 20).

15. The specification teaches that the administration of particular $A\beta_{42}$ (AN1792) fragments with an immunogenic adjuvant reduces β-amyloid levels within the brains of transgenic PDAPP mice. These mice exhibit Alzheimer type over production and build up of β-amyloid within the brain [Chapman (21/28 December 2000) "Model Behavior." Nature **408**: 915-916]. However, administration of $A\beta_{42}$ to Alzheimer's patients is not predictive of how administration of PrP affects patients with prion-related diseases or any given amyloid dependent disorders. There are no examples directed to PrP, diseases caused by PrP, or art-accepted PrP animal models.

16. Since the specification fails to provide any guidance for the successful therapeutic use of PrP and since resolution of the various complications in regards to prion diseases is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. One skilled in this art would be expected to reasonably doubt that the claimed pharmaceutical composition would work due to the following obstacles: Specific biological actions/activities that the antigenic composition of PrP and an adjuvant would effect; How does the immunogenic effect on amyloid deposition relate to symptoms of prion disorders. The specification does not provide guidance on how to overcome expected obstacles. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed [see Akiyama *et al.* (2000) "Inflammation and Alzheimer's disease." Neurobiology of Aging **21**: 383-421].

17. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the pharmaceutical composition comprising PrP in a patient. Additionally, a person skilled in the art would recognize that predicting the efficacy of using an immunogenic composition *in vivo* based solely on the performance of a different, unrelated immunogenic preparation is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed pharmaceutical compositions in therapies, such a disclosure would not be considered enabling since the state of prior diseases is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;

(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

18. The following references are cited herein to illustrate the state of the art of prion precursor protein (PrP).

19. Regarding the breadth of the claims, Goldfarb and Brown (1995) "The Transmissible Spongiform Encephalopathies." Annu. Rev. Med. **46**: 57-66 teaches that prion disease also known as transmissible spongiform encephalopathies (TSEs) encompasses kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and fatal familial insomnia (Abstract). All of these diseases share a common element of a prion protein however the diseases are caused by different mutations and various isoforms may or may not be infectious (Table 1 and Table 2). In addition, Kovács *et al.* (2002) "Mutations of the Prion Protein Gene." J. Neurol. **249**: 1567-1582 teaches that different mutations of the prion protein gene are responsible for different diseases with differing ages of onset and severity (Tables 1 and 2; Figures 4 and 5). Thus the skilled artisan is confronted with an undue burden of experimentation and unpredictability on how each individual isoform and/or mutation will affect the immune system of a patient [see also Elan Press Release (18 January 2002) pp. 1-3].

20. On the nature of the invention, Wisniewski *et al.* (2002) "Therapeutics in Alzheimer's and Prion Diseases." Biochemical Society Transactions **30**(4): 574-578 teaches that the use of a nontoxic form of amyloid protein is crucial for the success of any immune based therapies for amyloidogenic diseases (pp. 577). Further Tal *et al.* (2003) "Complete Freund's Adjuvant Immunization Prolongs Survival in Experimental Prion Disease in Mice." Journal of

Neuroscience Research **71**: 286-290 teaches that complete Freund's adjuvant alone had the same immunoprotective effect as CFA+immunogenic PrP^{Sc} peptides in a mouse model (Figures 1 and 2; pp. 289). Thus the skilled artisan is confronted with a level of unpredictability as to how the PrP or adjuvant used will affect the patient and whether or not the PrP must be genetically modified to escape possible toxic side effects.

21. On the state of the prior art, Smits and Schreunder (1997) and Aguzzi & Weissmann (23 October 1997) "Prion research: the next frontiers." Nature **389**: 795-798 suggest that one method of acquiring a prion-based disorder, such as Transmissible Spongiform Encephalopathy or Creutzfeldt-Jakob disease, may be the consumption or administration of a prion precursor protein, such as PrP, to an animal. Therefore, instead of eliciting a beneficial immune response to alleviate the PrP disorder, the administration of the PrP protein or fragment may cause a prion disorder.

22. Concerning the level of predictability in the art, Diomede *et al.* (1996) "Activation effects of a prion protein fragment [PrP-(106-126)] on human leucocytes." Biochem. J. **320**: 563-570 teaches that a fragment of PrP, residues 106-126 is toxic to neurons and astrocytes *in vitro* but stimulates neutrophils, monocytes, and lymphocytes, also *in vitro* (Figure 6). Thus PrP may be toxic to some cells but not to others. Also, Diomede *et al.* noted that immune cells may be able to survive the toxic effects of PrP because they are constantly dividing thus allowing for their numbers to be replenished following exposure to PrP (pp. 569). Thus the skilled artisan is confronted with an unpredictability of the effects of prion precursor protein and its fragments on cells.

23. In light of the instant Specification's teachings, Sigurdsson *et al.* (July 2002) "Immunization Delays the Onset of Prion Disease in Mice." American Journal of Pathology **161**(1): 13-17 teaches that the active immunization of mice with recombinant PrP in a pharmaceutical composition with Freund's adjuvant subcutaneously administered delayed the onset of prion disease in said mice (Figures 1 and 2). However, Sigurdsson *et al.* cautions that:

> "There are a number of potential toxic side effects that will require further animal and *in vitro* experimentation. One source of toxicity is from the immunogen that it used. In our Alzheimer's disease vaccine development studies we altered the Aβ sequence making it nonfibrillogenic and nontoxic, while maintaining or increasing its immunogenicity, reducing the potential of this toxicity. Similar types of alterations are underway to limit any potential toxicity from using the native PrP sequences as an immunogen." (pp. 16)

Thus the skilled artisan does not have sufficient guidance from the instant Specification to alter/mutate/change the native PrP into an acceptable form for use on patients.

24. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from β-amyloid experiments to the *in vivo* treatment of prion disorders as exemplified in the references above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

25. Claims **1-6** and **9-10** are rejected under 35 U.S.C. 102(b) as being anticipated by Prusiner *et al.* (November 1993) "Ablation of the prion protein (PrP) gene in mice prevents scrapie and facilities production of anti-PrP antibodies." PNAS **90**: 10608-10612. Prusiner *et al.* teaches a pharmaceutical composition comprising PrP^{Sc} with complete Freund's adjuvant which can induce an immunological response thus meeting the limitations of claims 1-6 and 9-10 (pp. 10609). It is noted that the instant Specification defines "AScr" as PrP^{Sc} or the infectious/pathological form of PrP (pp. 20).

26. Claims **1-6** and **9-10** are rejected under 35 U.S.C. 102(e) as being anticipated by US 5846533 (8 December 1998) Prusiner *et al.* US 5846533 teaches a pharmaceutical composition comprising $MoPrP^{Sc}$ emulsified in complete Freund's adjuvant which is capable of producing antibodies, an immune response thus meeting the limitations of claims 1-6 and 9-10 (Col. 29 lines 44-67). It is noted that the instant Specification defines "AScr" as PrP^{Sc} or the infectious/pathological form of PrP (pp. 20).

Summary

27. Claims **1-10** are hereby rejected.

28. The following articles, patents, and published patent applications were found by the Examiner during the prior art search and are here made of note:

a. US 5750361 (12 May 1998) Prusiner *et al.*

b. US 5753624 (19 May 1998) McMichael & Kline

c. US 5851996 (22 December 1998) Kline

d. US 2002/0168377 A1 (14 November 2002) Schaetzl

e. US 2002/0197258 A1 (26 December 2002) Ghanbari & Ghanbari

f. US 2002/0094335 A1 (18 July 2002) Chalifour *et al.*

g. US 2002/0132268 A1 (19 September 2002) Chang & Lu

h. US 2001/0021769 A1 (13 September 2001) Prusiner

i. WO 97/10505 (20 March 1997) Prusiner *et al.*

j. Weldon *et al.* (1 November 1996) "Neurotoxicity of Aβ Peptide: Confocal Imaging of cellular Changes Induced by β-Amyloid in Rat CNS *In Vivo*." Society for Neuroscience ABSTRACTS

k. Frautschy *et al.* (October 1991) "Effects of Injected Alzheimer β-amyloid cores in rat brain." PNAS **88**: 8362-8366

l. Monsonego *et al.* (28 August 2001) "Immune hyporesponsiveness to amyloid β-peptide in amyloid precursor protein transgenic mice: Implications for the pathogenesis and treatment of Alzheimer's disease." PNAS **98**(18): 10273-10278

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
July 10, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER